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Air Pollution and Pulmonary Tuberculosis: A Nested Case-Control Study among Members of a Northern California Health Plan

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Running title: Air pollution and pulmonary TB in Northern California

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ABSTRACT

Background: Ecologic analyses, case-case comparisons, and animal experiments suggest positive associations between air pollution and tuberculosis.

Objectives: We evaluated this hypothesis in a large sample which yields results more applicable to the general population.

Methods: We conducted a case-control study nested within a cohort of Kaiser Permanente of Northern California members. All active pulmonary tuberculosis (TB) cases newly diagnosed from 1996-2010 (n=2309) were matched to two controls (n=4604) by age, gender, and race/ethnicity on the index date corresponding with the case diagnosis date. Average individual-level concentrations of carbon monoxide (CO), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), ozone (O_3), and particulate matter with aerodynamic diameter <2.5μm ($PM_{2.5}$) and 10μm (PM_{10}) for two years prior to diagnosis/entry into the study were estimated using measurements from the California Air Resources Board monitor closest to the subject's residence.

Results: In single-pollutant adjusted conditional logistic regression models the pulmonary TB odds ratios (95% confidence interval) for the highest quintile (vs. lowest) were 1.50 (1.15, 1.95) for CO and 1.42 (1.10, 1.84) for NO_2. Corresponding estimates were higher among never ((1.68 (1.26, 2.24) than ever smokers (1.19 (0.74, 1.92)) for CO. In contrast, for NO_2, estimates were higher among ever (1.81 (1.13, 2.91)) than never smokers (1.29 (0.97, 1.71)). O_3 was inversely associated for smokers (0.66 (0.43, 1.02)) and never smokers (0.65 (0.52, 0.81)). No other consistent patterns were observed.

Conclusions: In this first U.S. nested case-control study on air pollution and pulmonary TB to our knowledge, we observed positive associations with ambient CO and NO_2, which require confirmation.

INTRODUCTION

Air pollution is a substantial cause of morbidity and mortality worldwide, resulting in major public health impacts and millions of dollars lost each year (Holgate et al. 1999; WHO 2011). Recent meta-analyses have revealed an association between indoor air pollution, primarily from biomass fuel combustion, and tuberculosis (TB) disease (Lin et al. 2007, Sumpter and Chandramohan 2013). Ecologic studies, including several conducted in the U.S., also suggest that TB is associated with ambient air pollution, including both short-term (Shilova et al. 2004) as well as long-term exposures (Iwai et al. 2005; Smith et al. 2014; Tremblay 2007). An ecologic study in Japan reported a correlation between annual total suspended particles in air and TB (Iwai et al. 2005). While exploring seasonal fluctuations of TB incidence in an ecologic analysis in Russia, Shilova et al. (2004) found that along with climatic factors, atmospheric pollutants (including NO, CO, and SO_2) were associated with TB incidence. In a recent study of 196 patients from two Los Angeles hospitals, a correlation was observed between annual small particle-size particulate matter ($PM_{2.5}$) and acid-fast bacilli (AFB) smear positive TB compared to AFB negative TB (Jassal et al. 2013). Howeve r, epidemiologic studies that consider a wider variety of individual-level air pollutant exposures in a large sample that is more generalizable to the general population are lacking.

Mycobacterium tuberculosis is the causative agent of TB. The immune system is most often able to contain this infection; however, weakened immunity, caused by HIV, diabetes, and a host of other factors, can cause TB to reactivate (i.e., progress from inactive to active infection) (Raviglione et al. 1995; WHO 2010). Biologically, air pollutants could be involved in the

reactivation of TB through altering macrophage function, thereby increasing susceptibility to developing active TB. Tumor necrosis factor (TNF)-α and interferon-gamma (IFN-γ) play a central role in containing and inhibiting the growth of mycobacteria (Döffinger et al. 2004; Flad et al. 1995; Fremond et al. 2005), but animal experiments on the effects of air pollution on cytokine expression in general (Saito et al. 2002a) and in response to mycobacterial infection (Hirmatsu et al. 2005; Saito et al. 2002b) both indicate decreased levels of these proteins. Long-term exposure to diesel exhaust has been shown to reduce TNF-α and IFN-γ production (Saito et al. 2002a,b), to decrease expression levels of IFN-γ and inducible NO synthase mRNAs, and increase the mycobacterial load in mice (Hiramatsu et al. 2005).

OBJECTIVES

This study aims to investigate whether exposure to criteria air pollutants (sulfur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO), ozone (O_3), particulate matter with aerodynamic diameter of 10 μm or less (PM_{10}), and particulate matter with aerodynamic diameter of 2.5 μm or less ($PM_{2.5}$)) are associated with increased risk of active pulmonary TB in a well-defined population of Northern California residents.

METHODS

Study Population. We conducted a nested case-control study of the association between air pollution and pulmonary TB disease among the members of Kaiser Permanente Northern California (KPNC), an integrated healthcare delivery system providing care to 3.3 million residents in the greater San Francisco, Oakland, San Jose, Sacramento, and Fresno areas. KPNC serves approximately 25-30% of the entire population in the geographic areas served. Cases

included all newly diagnosed active pulmonary TB among adult KPNC members. Cases were individuals, between January 1996 and December 2010, with either: (1) a new clinical diagnosis and prescription for at least 30 days of four more anti-tuberculosis medications including isoniazid, rifampin, ethambutol, and pyrazinamide; or (2) an initial positive TB culture. For cases, diagnosis date, use of anti-TB drugs and relevant laboratory assays were abstracted from the KPNC clinical data bases. Controls, selected from KPNC members free of TB on the index date of diagnosis of the case, were matched to cases (2:1) by age, gender, and race/ethnicity (non-Hispanic white, Black, Asian, other). All cases and controls were KPNC members for a minimum of 2 years prior to entry into the study. Institutional Review Board approval was obtained from KPNC and the University of North Carolina at Chapel Hill prior to initiating research. This study was limited to the analysis of existing data that involved no direct interaction with subjects and therefore met criteria for waiver of informed consent.

Exposure Assessment. Exposures estimates for each individual were determined using average ambient concentrations of $PM_{2.5}$, PM_{10}, O_3, NO_2, CO, SO_2 from all relevant monitors operating in California in the 24 months prior to diagnosis/entry into the study. Based on the assumption that air pollution acts to increase susceptibility to develop pulmonary TB upon exposure to *Mycobacterium tuberculosis*, we *a priori* posited that the etiologically-relevant exposure window was the period within 24 months prior to initial infection with TB (Raviglione et al. 1995; WHO 2010). Pollutant concentrations were obtained using monitoring stations from California's State and Local Air Monitoring Network (http://www.arb.ca.gov/aqd/netrpt/netrpt.htm) with at least 75% completeness in each month. Monitors with 25% or more incomplete data for a month were not included in the analysis and

therefore pollutant exposure measurements obtained from these monitors were recoded as missing and were not included in the analysis for that pollutant. The Interagency Monitoring of Protected Visual Environments (IMPROVE 2012) Network, which provides additional coverage of $PM_{2.5}$ in less populated areas of the state, was included to supplement $PM_{2.5}$ measurements, since state and local agencies only began monitoring $PM_{2.5}$ in 1999.

To assess individual-level air pollution exposure, geocoded patient home addresses (current and up to two years prior to diagnosis) were assigned the pollutant concentration of the closest available monitor (see Figures S1-S6 for the distribution of monitors in California). For each study participant, monthly exposures were estimated for each residence of record during the 24 months prior to diagnosis/entry into study, and then added together in order to calculate the average of the aggregate exposures. In addition, we assigned average 8-hour values for CO and O_3 (consistent with the values used for the National Ambient Air Quality Standards (U.S. EPA 2008b)) from these same monitors closest to each participant's home address.

Potential individual-level confounders and effect measure modifiers were ascertained from electronic clinical databases of KPNC, including data on age, gender, race/ethnicity, length of KPNC membership, cigarette smoking, alcohol hospitalization (defined as any record of hospitalization in which excessive alcohol intake/abuse is documented within the electronic clinical data), HIV status, co-morbidity (diabetes, COPD, renal dialysis), and residential address history. To examine the potential role of smoking on the association between air pollution and pulmonary TB, a variable was constructed from all smoking information recorded in the KPNC electronic clinical database; if smoking was indicated anywhere in records, the subject was considered an ever smoker, otherwise the subject was considered a never smoker. Additionally,

using the 2000 U.S. Census data, block level continuous (median household income, percent foreign born, and percent with more than high school education) variables were created as indicators of socioeconomic status at diagnosis/study entry for factors not routinely collected at KPNC.

Statistical Analysis. We used conditional logistic regression analysis, adjusting for all matching factors (age, gender, and race/ethnicity), to estimate the odds ratios (OR) and 95% confidence intervals (CI) for the association between pulmonary TB and each average air pollutant concentration (SO_2, NO_2, CO, O_3, PM_{10} and $PM_{2.5}$) assigned to each individual for the 24 months prior to diagnosis date/date of study entry. Exposure levels below the 20th percentile were used as the referent category for each pollutant. Individual monthly air pollutant averages were considered in the 24 months prior to diagnosis (to explore variations with lag-time), but our conclusions did not differ from the 24-month averages, and thus the results for the 24-month averages are shown.

Potential confounders and effect modifiers were identified through reviewing current literature and examining causal diagrams to clarify relationships between factors (Rothman et al. 2012). Potential confounders were further assessed using a greater than 10% change in estimate criterion (Greenland 1989) for several risk factors that could potentially confound the relationship between air pollution and pulmonary TB: cigarette smoking, length of KPNC membership, median household income, percent foreign born in census block, education in residential census block, alcohol hospitalization, diabetes, and HIV status. Using this criterion, no factors were found to confound the air pollution-pulmonary TB associations and were

therefore not included in the final analysis. Final models only included the matching factors (age, gender, and race/ethnicity).

Potential effect modifiers (cigarette smoking, alcohol hospitalizations, diabetes, COPD, HIV status, renal dialysis (all categorized as ever/never), and percent foreign born in census block (continuous)) were further assessed using likelihood ratio tests (LRTs) (Hosmer and Lemeshow 1989). To determine the presence of effect modification, we compared LRTs from models with and without interaction terms included in the conditional logistic regression model. Effect modification was considered present if the LRT differed at a significance level of <.10. Only smoking met this criteria, and thus only these stratum-specific ORs are shown.

A multi-pollutant analysis for air pollution and pulmonary TB association was also considered. All analyses were conducted using SAS (version 9.3; SAS Institute, Cary, NC).

RESULTS

Characteristics of pulmonary TB cases and matched controls nested within the KPNC membership are summarized in Table 1. We identified 2309 cases of pulmonary TB, and 4604 controls matched 2:1 to cases by age, gender, and race/ethnicity, which were drawn from the existing KNPC membership during the study period, 1996-2010. Less than a third (2028) of the participants were classified as ever smokers. The study population was split equally by gender, though a larger percentage of males were considered ever smokers than females (44.1% vs. 19.9% among cases and 36.0% vs. 20.1% among controls). As expected, never smokers were younger in age than ever smokers (median = 47 and 54 years, respectively). The proportion of Asians and Hispanics within this study is consistent with the racial/ethnic distribution of residents in this geographic area, as well as the at-risk population for TB in the U.S. (CDC

2011).

As shown in Table 2, average ambient air pollution concentrations in the 24 months prior to the diagnosis date varied greatly for participants. Median air pollution concentrations were the same among never smokers and ever smokers for all pollutants, with the exception of CO. Ambient CO concentrations measured in the 24 months prior to pulmonary TB diagnosis/entry into the study were slightly higher for never smokers than ever smokers. Because the number and the location of available monitors within the network varied, particularly for $PM_{2.5}$ which was not routinely monitored until 1999, the number of cases and controls with available pollutant data also varied over the study (see Table 3). As shown in Table 4, Spearman's correlation air-pollutant averages in the 24 months prior to date of diagnosis showed only moderate correlations between pollutants. The strongest correlation observed between ambient averages of air pollutants was seen for PM_{10} and $PM_{2.5}$ (r=0.61).

Pulmonary TB. Figure 1 and Table 5 present the odds ratios (ORs) and 95% confidence intervals (CI) for the single-pollutant model associations between air pollution, in quintiles, and pulmonary TB in the 24 months prior to diagnosis date/study entry among all cases and matched controls. All effect estimates are adjusted for the matching factors of age, gender, and race/ethnicity. There was no evidence of association between each of the criteria pollutants $PM_{2.5}$, PM_{10}, and SO_2, and pulmonary TB.

As shown in Figure 1 and Table 5, CO and NO_2 were positively associated with pulmonary TB for the two highest quintiles of exposure in single-pollutant models. For example, the strongest positive effect estimates among all subjects (ever and never smokers combined) for

the association of ambient air pollution and pulmonary TB were observed for CO (OR=1.50 (95% CI: 1.15, 1.95)), as shown in Table 5. Additionally, as measured concentrations of CO exposure increased, the associated odds of pulmonary TB increased. NO_2 was also positively associated with pulmonary TB, with an apparent dose-response pattern between exposure and pulmonary TB odds.

An inverse association was observed for 8h O_3 and pulmonary TB, with all exposures above the lowest quintile resulting in decreases in the effect estimates, which was evident in the single-pollutant models. For example, compared to those in the lowest quintile of O_3 exposure, those in the highest quintile, compared to the lowest, had a considerable decrease in risk of pulmonary TB (OR= 0.66 (95%CI: 0.55, 0.79)).

We also considered multi-pollutant models (Table 5). Though the results of the single- and multi-pollutant models are generally consistent, effect estimates were attenuated. For instance, in multi-pollutant models the OR for the highest quintile of CO exposure was 1.21 (95% CI: 0.80, 1.83). Also, the dose-response pattern observed in the single-pollutant model for the association between CO and pulmonary TB became non-monotonic in the multi-pollutant models. While the dose-response pattern between NO_2 exposure and pulmonary TB odds in was still observed in multi-pollutant models, multi-pollutant CIs included the null value.

Pulmonary TB Stratified by Smoking. In single-pollutant models, cigarette smoking was found to be an effect modifier of the association ambient CO and pulmonary TB (p=0.10) for the interaction on multiplicative scale. Following stratification, a dose-response pattern persisted among never smokers and the effect estimates for the highest quintiles of 8hr CO

exposure, compared to the lowest, were more pronounced among never smokers (OR=1.68 (95% CI: 1.26, 2.24)) than ever smokers (OR=1.19 (95% CI: 0.74, 1.92), as shown in Figure 2 and Table 6.

Once stratified on smoking status, the dose-response pattern previously observed in non-stratified models was less pronounced. The association between NO_2 and pulmonary TB, in the single-pollutant models, was more pronounced among ever smokers (OR=1.81 (1.13, 2.92) for the highest vs. the lowest quintile of exposure), than among never smokers (OR=1.29 (0.97, 1.71)), but based on LRT heterogeneity in the effect estimates was not statistically significant (p=0.19).

Upon stratification by smoking status, the strength of the inverse association was similar among both non-smokers and smokers in the single-pollutant models for the association between O_3 and pulmonary TB.

Stratified analyses of the multi-pollutant model estimates by cigarette smoking status yielded results similar to the single pollutant analysis (see Table S1).

DISCUSSION

In this sample of Northern California residents (2309 cases and 4604 controls), which is, to the best of our knowledge, the first large U.S. study within a well-defined population to assess the potential associations between individual-level estimates of the criteria air pollutants and pulmonary TB, exposure to average 8-hour CO concentrations in the highest quintile during the 24 months prior to diagnosis was associated with a 50% elevation in the odds of developing

pulmonary TB (95% CI: 15, 95%) relative to the odds among those in the lowest quintile of exposure. When the analysis was stratified by smoking status, effect estimates for the association between CO and pulmonary TB were slightly stronger for never smokers and weaker or null for ever smokers. Positive associations were also noted for NO_2, although the magnitude of the association was stronger in smokers than in never smokers. In addition, effect estimates were reduced by about one-third for O_3. No consistent associations were observed among the other pollutants studied, including $PM_{2.5}$, PM_{10}, and SO_2.

Multi-pollutant analyses were conducted to assess the association of combined exposure to several air pollutants on odds of pulmonary TB. While the multi-pollutant model may account for possible mutual confounding between pollutants, there is the potential for variance inflation and bias in analyses that adjust for multiple pollutants if these are highly correlated (Rothman et al. 2012 pp139-142; Schisterman 2009). Since it is unclear which model resulted in the least biased estimates, both single- and multi-pollutant model results were presented. Several of the effect estimates from the multi-pollutant models for the association between air pollution and pulmonary TB are attenuated toward the null value, with wider confidence intervals than in the single-pollutant model; however, the effect estimates still reflect the same patterns of association in general. These results emphasize the need for more precise effect estimates, as well as improved assessment of both air pollution exposure concentrations and smoking status.

The associations observed in CO are consistent with other available evidence on this issue. Exposure to ambient CO in the U.S. in this setting is primarily a marker of exposure to combustion products and secondary vehicular traffic (U.S. EPA 2010), and experimental studies show that diesel exhaust affects immune processes that inhibit TB in mice (Hirmatsu et al. 2005;

Saito et al. 2002b). A previous study of combustion products is consistent with the hypothesis that coal consumption, using annual historical statistics, may be linked to TB since both have followed similar trends in the U.S., Canada, and China (Tremblay 2007), though this is a crude ecological comparison (Tremblay 2007).

In our study, risk of pulmonary TB was also positively associated with exposure to NO_2. This gaseous pollutant is produced primarily from combustion sources, such as motor vehicle exhaust, and electric generating units (U.S. EPA 2008b). Individuals living near busy roads are therefore more likely to be exposed to NO_2 pollution (Gilbert et al. 2007, U.S. EPA 2008b) and may disproportionately suffer from any related health effects (EPA 2008b, HEI 2010, Oosterlee et al. 1996). Although individual pollutant exposure depends predominantly on local outdoor concentrations, indoor pollution such as smoking and using gas appliances may alter exposure levels (U.S. EPA 2008b). It is also possible that the associations with NO_2 may represent exposure to traffic related air pollution rather than exposure to NO_2 specifically.

In this study, an inverse association was seen with O_3 and pulmonary TB, with all exposures above the lowest quintile resulting in decreases in pulmonary TB risk. This observed relationship between O_3 concentrations and pulmonary TB is not entirely unexpected as levels of ambient O_3 and NO_2 are bonded by chemical coupling. In the presence of sunlight nitrogen is depleted in the formation of O_3 (Clapp 2001, U.S. EPA 2013). As a result, individuals exposed to higher levels of NO_2 often experience lower levels of O_3, particularly along high traffic areas (Jerrett et al. 2005, Lipsett et al. 2011).

We observed no consistent association between $PM_{2.5}$ and pulmonary TB. We are aware

of one previous study (Jassal et al. 2012) which reports a positive association between ambient $PM_{2.5}$ and the odds of having acid fast bacilli detected (versus not detected) on a sputum smear (an indication of active TB), however this finding is based on less than 200 hospital patients in Los Angeles, California. In contrast, our results are based on nested case-control study data with 6913 subjects that are broadly representative of the Northern California population from which they are drawn, and our cases are compared to a control population that did not have active TB. Additional studies are needed to elucidate possible associations between $PM_{2.5}$ and active pulmonary TB.

Assigning individual average exposures by relying on the ambient air monitoring closest to the participant's home likely introduces some exposure misclassification. This issue may be particularly relevant to CO assessments, because of considerable spatial variability in ambient CO concentrations (U.S. EPA 2010). Further, exposure misclassification might have occurred as a result of variations in residential ventilation systems, levels of physical activity, or time spent outdoors, away from home or traveling by car outside of their residential area. The latter is important as considerable CO exposure can be experienced while driving or riding in vehicles (U.S. EPA 2010). However, these potential sources of error are common to many epidemiologic studies focused on assessing the health effects associated with air pollution, which have also used our approach to estimate individual-level ambient concentrations (Brauer et al. 2008; Brunekreef et al. 2009; Lipsett et al. 2011). These errors are perhaps non-differential, given that exposure estimates for our cohort of Kaiser subjects were constructed at CARB (by CG), without knowledge of the subjects' outcome status, by matching the subject address recorded in each subject's medical record with the air pollutant concentrations recorded at the nearest monitor.

Also, cases and controls, which were nested in the Kaiser cohort and required to have at least two years of Kaiser membership for study eligibility, and we adjusted for census-block derived education and income, all of which would help to reduce any differential misclassification bias associated with residential location and hence exposure estimation. All of these issues would improve the likelihood of non-differential exposure misclassification, which may bias results toward the null which may bias results toward the null (Rothman et al. 2012). However, differential misclassification is possible, given that assignment of exposure status was not dichotomous, and thus spurious associations could arise. Perhaps by improving exposure estimation through the use of more sophisticated methods, such as land use regression or kriging (Hoek et al. 2008; Jerrett et al. 2005), future studies could enhance our ability to determine the true magnitude of the air pollution-TB association.

To examine the potential role of smoking on the association between air pollution, subjects were considered never smokers if there was no indication of smoking anywhere in records. This method of categorizing smokers may have resulted in underestimation of smoking prevalence in this study population if smoking status is underreported in the clinical data. This underestimation could lead to a spurious result when smoking status was included in the analyses if the error was differential by air pollution exposure status. However, assignment of smoking status was made blinded to case status and air pollution exposure status, thus differential misclassification of smoking seems unlikely. Further, for study eligibility, cases and controls were matched on age and required to have Kaiser membership of at least two years in duration, both of which would help to reduce – although not entirely eliminate – the likelihood of differential exposure misclassification due to cohort or acculturation differences. With non-

differential error of a covariate would result in attenuation of the effect estimates (Rothman et al. 2012).

Recent immigration status, a factor that puts individuals at disproportionately increased risk of TB in the U.S. (CDC 2011), was not available for cases and controls in this population. We instead included percent of the census block that was foreign born in our early statistical models, but the covariate did not confound our associations. Although use of this proxy is inexact, mandatory screening confirms that all immigrants should be free of active TB upon entry into the U.S. (Liu et al. 2009). Furthermore, to ensure that recent immigrants (those at the highest risk) were screened out of the study and that we captured cases of TB activated within the U.S., we implemented a two-year KPNC membership requirement for subject eligibility.

This nested case-control study conducted within a large well-defined population has several advantages. The KPNC membership provides the clear sampling framework for control selection and is broadly representative of the population-at-large. However, the KPNC membership is somewhat better educated than the surrounding geographic population, has fewer individuals in the income extremes, and has a lower prevalence of smokers (Gordon 2006). On the other hand, the uniform access to health care in this population minimizes the potential for selection bias, and the availability of detailed clinical data allowed us to explore potential confounding and effect modification of numerous risk factors associated with TB including COPD, alcohol hospitalizations, diabetes, renal dialysis, and immunosuppressive conditions including HIV (CDC 2011; Liu et al. 2009). Finally, the availability of the criteria air pollution data permitted us to construct ambient exposure concentrations during the 24-month period prior to a diagnosis of pulmonary TB for all KPNC study subjects with available pollutant data, which

is considered the critical window between exposure to mycobacteria and development of active pulmonary TB (Raviglione et al. 1995; WHO 2010).

The persistence of ambient air pollution remains a major public health problem, as millions worldwide die each year from causes directly related to air pollution (WHO 2011). While levels of air pollution have continually dropped in the U.S. and other developed countries in recent years, levels in developing countries remain high and are even increasing in many areas (WHO 2011). Many of the same countries with high levels of air pollution are also burdened with the highest levels of TB and increasing prevalence of cigarette smoking (Cohen and Mehta 2007; Hassmiller 2006).

In conclusion, our results showed positive associations between ambient concentrations of CO and NO_2 and risk of pulmonary TB among residents in Northern California. To our knowledge this is the first large, nested case-control study with individual-level estimates of air pollution concentrations conducted in the U.S., thus future studies in places similar to the U.S. (low TB rates and air pollution levels) using a larger sample size and improved characterization of smoking status (both allowing for examination within various smoking strata) are needed to confirm our findings. Studies are also needed in countries outside the U.S. which experience higher rates of TB and increased exposure to outdoor air pollution. Given that large number of people worldwide infected with *Mycobacterium tuberculosis* and exposed to high air pollution concentrations, any association between air pollution and TB is of considerable public health importance, as attention to the impact of air quality may contribute to global TB control.

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Table 1. Distribution of characteristics of pulmonary tuberculosis disease (TB) cases and matched controls nested within the Kaiser Permanente of Northern California (KPNC) membership, 1996-2010.

Characteristics	**All**		**Ever Smokers**		**Never Smokers**	
	Cases n=2309	**Controls** n=4604	**Cases** n=737	**Controls** n=1291	**Cases** n=1572	**Controls** n=3313
ECD Demographic Factors						
Gender						
Male	1144 (49.6%)	2291 (49.8%)	505 (68.5%)	825 (63.9%)	639 (40.7%)	1466 (44.3%)
Female	1165 (50.4%)	2313 (50.2%)	232 (31.5%)	466 (36.1%)	933 (59.4%)	1847 (55.6%)
Age						
21-34	512 (22.1%)	1000 (21.7%)	94 (12.8%)	202 (15.7%)	418 (26.6%)	798 (24.1%)
35-49	648 (28.1%)	1271 (28.1%)	178 (24.1%)	305 (23.6%)	470 (29.9%)	966 (29.2%)
50-64	631 (27.3%)	1270 (27.6%)	268 (36.4%)	418 (32.3%)	363 (23.1%)	852 (25.7%)
65+	518 (22.4%)	1063 (23.1%)	197 (26.7%)	366 (28.4%)	321 (20.4%)	697 (21.0%)
Race/Ethnicity						
Non-Hispanic White	402 (17.4%)	811 (17.6%)	175 (23.7%)	288 (22.3%)	227 (14.4%)	523 (15.8%)
Black	184 (8.0%)	356 (7.7%)	79 (10.7%)	135 (10.5%)	105 (6.7%)	221 (6.7%)
Asian	894 (38.7%)	1801 (39.1%)	222 (30.1%)	371 (28.7%)	672 (42.7%)	1430 (43.2%)
Hispanic	451 (19.5%)	912 (19.8%)	142 (19.3%)	263 (20.4%)	309 (19.7%)	649 (19.6%)
Other	150 (6.5%)	298 (6.4%)	56 (7.6%)	124 (9.6%)	94 (6.0%)	174 (0.5%)
Unknown	228 (9.9%)	426 (9.3%)	63 (8.5%)	110 (8.5%)	165 (10.5%)	316 (9.5%)
Length of Enrollment						
2-5 years	768 (33.3%)	1493 (32.4%)	220 (29.9%)	378 (29.3%)	548 (34.9%)	1115 (33.7%)
5-10 years	628 (27.2%)	1222 (26.5%)	186 (25.2%)	321 (24.9%)	442 (28.1%)	901 (27.2%)
10-15 years	332 (14.4%)	640 (13.9%)	104 (14.1%)	202 (15.7%)	228 (14.5%)	438 (13.2%)
15+ years	581 (25.2%)	1249 (27.1%)	227 (30.8%)	390 (30.2%)	354 (22.5%)	859 (25.9%)

Census Block Demographic Factors						
Median Household Income						
Median	$60,781	$61,443	$57,361	$59,077	$62,143	$62,566
(IQR)	($46k-$77k)	($46k-78k)	($44k-$72k)	($44k-$76k)	($47k-$79k)	($47k-79k)
Percent Foreign Born						
Median	26.3	21.9	24.4	19.6	27.0	22.8
(IQR)	(15.0-41.0)	(12.5-37.6)	(13.4-40.0)	(11.3-34.2)	(15.7-14.1)	(13.0-38.4)
More than High School Education						
Median	63	64.2	61.6	63.1	63.2	64.8
(IQR)	(49.4-75.1)	(50.3-76.8)	(48.4-73.2)	(50.0-75.6)	(50.4-75.7)	(50.6-77.1)
ECD Medical History						
Any Tuberculosis Risk Factors						
None	1292 (56.0%)	3087 (67.1%)	344 (46.7%)	757 (58.6%)	948 (60.3%)	2330 (70.3%)
COPD	856 (37.1%)	1298 (28.2%)	324 (44.0%)	433 (35.5%)	532 (33.8%)	865 (26.1%)
Alcohol Hospitalization	107 (4.6%)	169 (3.7%)	84 (11.4%)	98 (7.6%)	23 (1.5%)	71 (2.1%)
Renal Dialysis	146 (6.3%)	153 (3.3%)	53 (7.2%)	74 (5.7%)	93 (5.9%)	79 (2.4%)
Immunological Prescriptions[a]	0	0	0	0	0	0
Diabetes	452 (19.6%)	557 (12.1%)	184 (25.0%)	208 (16.1%)	268 (17.1%)	349 (10.5%)
HIV +	49 (2.1%)	13 (0.3%)	24 (3.3%)	6 (0.5%)	25 (1.6%)	7(0.2%)

Abbreviations: ECD = electronic clinical database; eIQR = interquartile range; COPD = chronic obstructive pulmonary disease; and HIV+ = human immunodeficiency virus positive.

[a]Immunological Prescriptions include immune compromising medications known to increase TB risk including glucocorticoids, infliximab, etanercept, adalimuma, certolizumab pegol (Cimzia), golimumab (Simponi) and chemotherapy drugs.

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Table 2. Distribution of ambient criteria air pollution concentrations averaged across a 24-month period prior to the pulmonary tuberculosis (TB) diagnosis/entry into study for cases/matched controls nested within the 1996-2010 KPNC membership with available pollutant monitoring data.

	N (%) with Pollutant Data		Percentile Distribution						
Air Pollutant	**Cases**	**Controls**	**Min**	**20th**	**40th**	**Median**	**60th**	**80th**	**Max**
Total population									
24h $PM_{2.5}$ ($\mu g/m^3$)	1842 (79.8)	3661 (79.5)	0.1408	8.5600	9.1840	9.6268	10.3324	11.6602	26.4783
24h PM_{10} ($\mu g/m^3$)	2309 (100.0)	4604 (100.0)	9.1000	18.3896	19.8733	20.6067	21.6487	24.4700	56.6082
24h SO_2 (ppm)	2248 (97.4)	4439 (96.4)	0.0001	0.0009	0.0011	0.0012	0.0013	0.0018	0.0039
24h NO_2 (ppm)	2309 (100.0)	4601 (99.9)	0.0003	0.0098	0.0133	0.0144	0.0151	0.0177	0.0390
8h O_3 (ppm)	2309 (100.0)	4604 (100.0)	0.0178	0.0279	0.0301	0.0315	0.0330	0.0378	0.0670
8h CO (ppm)	2309 (100.0)	4598 (99.9)	0.0983	0.5481	0.6793	0.7656	0.8760	1.1114	3.0572
Ever Smokers									
24h $PM_{2.5}$ ($\mu g/m^3$)	617 (83.7)	1044 (80.9)	0.1408	8.5701	9.2355	9.6085	10.3507	11.7043	21.9646
24h PM_{10} ($\mu g/m^3$)	737 (100.0)	1291 (100.0)	9.1000	18.3547	19.8007	20.5427	21.5647	24.4560	48.6473
24h SO_2 (ppm)	716 (97.2)	1249 (96.8)	0.0001	0.0008	0.0011	0.0012	0.0013	0.0018	0.0038
24h NO_2 (ppm)	737 (100.0)	1291 (100.0)	0.0003	0.0100	0.0133	0.0142	0.0149	0.0174	0.0339
8h O_3 (ppm)	737 (100.0)	1291 (100.0)	0.0178	0.0279	0.0300	0.0315	0.0331	0.0382	0.0670
8h CO (ppm)	737 (100.0)	1289 (99.9)	0.0983	0.5276	0.6628	0.7441	0.8447	1.0882	1.9490
Never Smokers									
24h $PM_{2.5}$ ($\mu g/m^3$)	1225 (77.9)	2617 (79.0)	0.1408	8.5589	9.1735	9.6268	10.3206	11.6480	26.4783
24h PM_{10} ($\mu g/m^3$)	1572 (100.0)	3313 (100.0)	10.3973	18.4381	19.8920	20.6708	21.7093	24.5191	58.6082
24h SO_2 (ppm)	1532 (97.5)	3190 (96.3)	0.0000	0.0009	0.0011	0.0012	0.0012	0.0018	0.0039
24h NO_2 (ppm)	1572 (100.0)	3310 (99.9)	0.0003	0.0098	0.0134	0.0144	0.0152	0.0178	0.0390
8h O_3 (ppm)	1572 (100.0)	3313 (100.0)	0.0182	0.0279	0.0301	0.0315	0.0330	0.0377	0.0670
8h CO (ppm)	1572 (100.0)	3309 (99.9)	0.2430	0.5537	0.6860	0.7805	0.8877	1.1213	3.0572

Table 3. Distance (mi.) of residence from closest ambient pollutant monitors for the KPNC cohort, 1996-2010.

Air Pollutant	N	Mean	Std. Dev.	Minimum	Maximum
24h $PM_{2.5}$	5503	7.63	5.91	0.15	48.70
24h PM_{10}	6913	6.05	4.24	0.11	35.35
24h SO_2	6687	14.93	10.74	0.14	49.50
24h NO_2	6910	6.45	4.78	0.11	45.91
8h O_3	6913	4.66	3.12	0.05	36.74
8h CO	6907	6.23	4.70	0.05	43.15

Table 4. Spearman correlation coefficients[a] for the estimates of cumulative ambient criteria air pollutant concentrations, 24-month average, among pulmonary tuberculosis (TB) cases and matched controls nested within the 1995-2010 KPNC membership.

Air Pollutant	24h $PM_{2.5}$	24h PM_{10}	24hr SO_2	24h NO_2	8h O_3	8h CO
24h $PM_{2.5}$	1	0.61	0.12	0.28	0.25	0.35
24h PM_{10}		1	0.09	0.33	0.09	0.42
24h SO_2			1	0.19	-0.24	0.30
24h NO_2				1	-0.33	0.23
8h O_3					1	-0.28
8h CO						1

[a]All coefficients statistically significant ($p<0.05$)

Table 5. Conditional logistic regression estimated adjusted[a] odds ratios (ORs) and 95% confidence intervals (CIs) for associations of pulmonary tuberculosis (pulmonary TB) and ambient criteria air pollutants concentrations, 24-month averages, among all cases and matched controls nested within the 1996-2010 KPNC membership.

Pollutant	Quintile	Single	Multi[b]
$PM_{2.5}$	1	ref	ref
	2	1.13 (0.90, 1.41)	1.17 (0.92, 1.49)
	3	1.09 (0.87, 1.37)	1.04 (0.84, 1.29)
	4	1.11 (0.87, 1.42)	1.10 (0.87, 1.39)
	5	0.94 (0.73, 1.23)	1.00 (0.83, 1.20)
PM_{10}	1	ref	ref
	2	0.89 (0.74, 1.06)	0.81 (0.65, 1.00)
	3	1.11 (0.93, 1.32)	1.00 (0.78, 1.28)
	4	0.93 (0.77, 1.11)	0.90 (0.72, 1.13)
	5	0.78 (0.65, 0.94)	0.73 (0.52, 1.01)
SO_2	1	ref	ref
	2	0.95 (0.79, 1.15)	0.91 (0.74, 1.12)
	3	0.93 (0.78, 1.12)	0.89 (0.73,1.09)
	4	1.05 (0.86, 1.29)	1.03 (0.84, 1.23)
	5	0.90 (0.73, 1.12)	0.91 (0.78, 1.06)
NO_2	1	ref	ref
	2	1.17 (0.93, 1.46)	1.06 (0.81, 1.39)
	3	1.17 (0.93, 1.48)	1.08 (0.80, 1.45)
	4	1.27 (1.01, 1.61)	1.09 (0.79, 1.50)
	5	1.42 (1.10, 1.84)	1.26 (0.85, 1.86)
O_3	1	ref	ref
	2	0.92 (0.78, 1.10)	0.91 (0.73, 1.14)
	3	0.95 (0.80, 1.14)	0.93 (0.74, 1.17)
	4	0.71 (0.59, 0.85)	0.65 (0.51, 0.84)
	5	0.66 (0.55, 0.79)	0.67 (0.49, 0.91)
CO	1	ref	ref
	2	1.04 (0.86, 1.24)	0.93 (0.75, 1.16)
	3	1.19 (0.98, 1.45)	1.12 (0.88, 1.43)
	4	1.33 (1.06, 1.68)	1.22 (0.90, 1.66)
	5	1.50 (1.15, 1.95)	1.21 (0.80, 1.83)

[a]Adjusted for the matching factors (age, gender, and race/ethnicity).

[b]Multi-Pollutant Model: SO_2+$PM_{10+}PM_{2.5}$+CO+NO_2+ O_3

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Table 6. Conditional logistic regression estimated adjusted[a] odds ratios (ORs) and 95% confidence intervals (CIs) for associations of pulmonary tuberculosis (pulmonary TB) and ambient criteria air pollutants concentrations, 24-month averages, among cases and matched controls nested within the 1996-2010 KPNC membership, stratified by smoking status.

Pollutant	Quintile	Never Smokers	Ever Smokers	*p*-Value[b]
$PM_{2.5}$	1	ref	ref	
	2	0.98 (0.75, 1.27)	1.57 (0.95, 2.58)	
	3	1.03 (0.79, 1.34)	1.22 (0.75, 2.00)	
	4	1.04 (0.78, 1.37)	1.28 (0.78, 2.11)	
	5	0.85 (0.64, 1.15)	1.13 (0.68, 1.89)	0.2812
PM_{10}	1	ref	ref	
	2	0.80 (0.65, 0.99)	1.12 (0.73, 1.70)	
	3	1.07 (0.87, 1.32)	1.19 (0.78, 1.80)	
	4	0.94 (0.76, 1.16)	0.90 (0.59, 1.37)	
	5	0.69 (0.55, 0.87)	1.01 (0.66, 1.56)	0.0854
SO_2	1	ref	ref	
	2	0.88 (0.70, 1.10)	1.15 (0.74, 1.79)	
	3	0.86 (0.69, 1.08)	1.11 (0.72, 1.73)	
	4	1.02 (0.80, 1.29)	1.14 (0.73, 1.79)	
	5	0.86 (0.67, 1.10)	1.01 (0.64, 1.58)	0.6422
NO_2	1	ref	ref	
	2	1.15 (0.89, 1.48)	1.24 (0.79, 1.97)	
	3	1.00 (0.77, 1.29)	1.66 (1.05, 2.63)	
	4	1.18 (0.91, 1.53)	1.57 (0.99, 2.49)	
	5	1.29 (0.97, 1.71)	1.81 (1.13, 2.92)	0.1860
O_3	1	ref	ref	
	2	0.91 (0.74, 1.12)	0.94 (0.62, 1.43)	
	3	0.98 (0.80, 1.21)	0.88 (0.58, 1.33)	
	4	0.68 (0.55, 0.85)	0.76 (0.50, 1.17)	
	5	0.65 (0.52, 0.81)	0.66 (0.43, 1.02)	0.8170
CO	1	ref	ref	
	2	1.02 (0.82, 1.27)	1.08 (0.70, 1.66)	
	3	1.25 (0.99, 1.58)	1.10 (0.71, 1.70)	
	4	1.36 (1.05, 1.77)	1.30 (0.83, 2.05)	
	5	1.68 (1.26, 2.24)	1.19 (0.74, 1.92)	0.0979

[a]Adjusted for the matching factors (age, gender, and race/ethnicity).

[b]p-Value of likelihood ratio test comparing model fit with and without inclusion of interaction terms

FIGURE LEGENDS

Figure 1. Conditional logistic regression estimated adjusted[a] odds ratios (ORs)[b] and 95% confidence intervals (CIs) for the associations of pulmonary tuberculosis (pulmonary TB) and quintile[c] in the estimates of ambient criteria air pollutants concentrations within the 24-month average prior to diagnosis or index date, among all cases and matched controls nested within the 1996-2010 KPNC membership. [a]Adjusted for the matching factors (age, gender, and race/ethnicity). [b]ORs relative to the lowest quintile; numeric data provided in Table 4. [c]See Table 2 for quintile cutpoints.

Figure 2. Conditional logistic regression estimated adjusted[a] odds ratios (ORs)[b] and 95% confidence intervals (CIs) for the associations of pulmonary tuberculosis (pulmonary TB) and quintile[c] in the estimates of ambient criteria air pollutants concentrations within the 24-month average prior to diagnosis or index date, among cases and matched controls nested within the 1996-2010 KPNC membership stratified by smoking status (ever vs. never smokers). [a]Adjusted for the matching factors (age, gender, and race/ethnicity). [b]ORs relative to the lowest quintile; numeric data provided in Table 4. [c]See Table 2 for quintile cutpoints

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Figure 1.

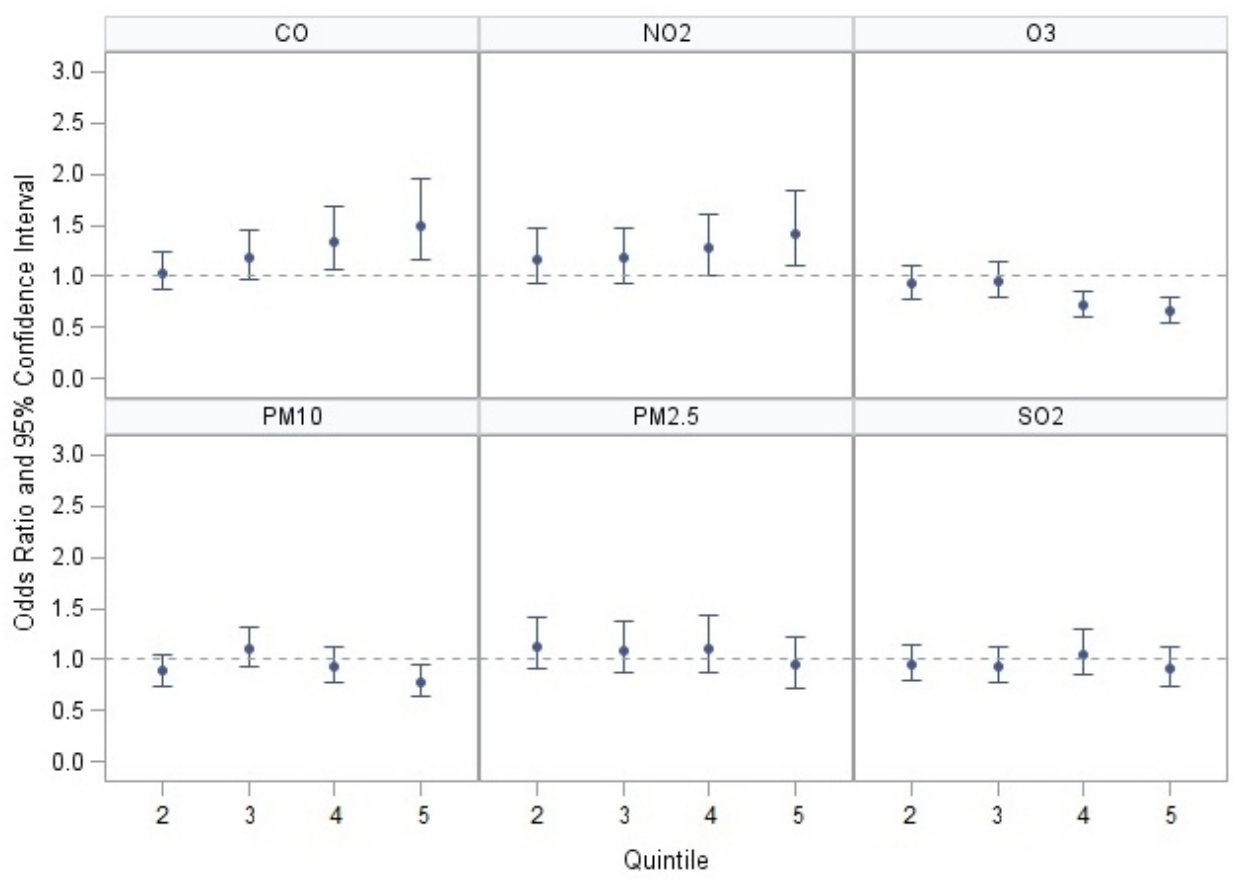

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Figure 2.